MYLAN TECHNOLOGIES INC.

December 1, 2004

**VIA HAND DELIVERY**

Division of Dockets Management Branch (HFA-305)
Food and Drug Administration
Room 1061
5630 Fishers Lane
Rockville, MD 20852

RE: Comments of Mylan Technologies Inc. on Docket No. 2004P-0472:
Refuse Final Approval to ANDA 76-258 For a Generic Fentanyl Transdermal System Under its Current Proposed Labeling

Dear Sir or Madam:

Mylan Technologies Inc. ("Mylan") submits these comments in response to the above-referenced Citizen Petition filed by Drs. Daniel Brookoff and Eric Voth ("Petitioners") on October 21, 2004 (the "Petition").

Mylan has an interest in the Petition because Mylan has submitted an abbreviated new drug application ("ANDA") for a generic fentanyl transdermal system ("FTS"), and the Petitioners have recommended to the Food and Drug Administration ("FDA") that it not approve Mylan's ANDA under its current proposed labeling.

The Petition should be denied because there is no increased risk of abuse or diversion associated with the design of the Mylan fentanyl transdermal system ("Mylan FTS"). The central premise of the Petition is that the Mylan FTS is a risk for abuse and diversion because it can be converted into a rapid release opioid product. That assertion is utterly without basis in fact. As set forth herein and in the accompanying declarations of H. Brian Goldman, M.D. and Gordon Flynn,

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Ph.D., the Petition is premised entirely on a misapprehension of the technology and science of the Mylan FTS. Potential abusers cannot convert the Mylan FTS into a rapid release opioid product and, therefore, it is not an attractive target for abuse or diversion.

The Petition offers no evidence to support the allegation that the Mylan FTS presents a risk for abuse and diversion. Instead, the Petition cites only speculation from John Coleman, a former DEA official who has since become a member of Janssen Pharmaceutica's speakers' bureau, as to possible ways in which the Mylan FTS could be abused. (Janssen Pharmaceutica currently sells the referenced drug, Duragesic®, which faces imminent generic competition because the Duragesic® patent expired on July 23, 2004.) The abuse scenario posited by the authors of the Petition based on Mr. Coleman's speculation could not occur, because the Mylan FTS cannot be converted into a rapid release system in that way. Therefore, Petitioners' references to abuse issues arising from the OxyContin® and Actiq® products which are or can easily be converted to forms that allow for rapid delivery of opioids are simply inapplicable to the Mylan FTS. Indeed, Janssen's recent introduction of a monolithic matrix in Europe for transdermal fentanyl delivery, which it asserts was motivated by an effort to improve safety, see Citizens' Petition 2004P-0506 (submitted November 12, 2004 by ALZA Corporation), is inconsistent with the position that the design of matrix systems gives rise to new methods of abuse.

- **The Development and Approval of the Mylan Fentanyl Transdermal System**

The Mylan FTS is a solid state monolithic matrix designed for transdermal delivery of fentanyl. It consists of fentanyl dispersed in silicone adhesive coated onto a suitable backing film with the delivery surface of the adhesive covered by a release liner. Like all systems designed to deliver drug products transdermally, the Mylan FTS is specifically made to permit delivery of drug through the barrier presented by the skin. To deliver drug product through the skin, the product is designed to maintain intimate contact with the skin surface. The fentanyl contained in the Mylan FTS is in the

form of fentanyl base. The fentanyl in the Mylan FTS is suspended in the adhesive of the patch, the majority of it undissolved. Because only drug in solution can pass through membranes like the skin, only that portion of the fentanyl base that is in solution is available to be delivered to and through the skin.

The Mylan FTS differs from Duragesic® in that the fentanyl in Mylan's system is dispersed throughout the adhesive layer itself rather than stored in a separate reservoir portion of the system. Duragesic®, in contrast, contains a reservoir separate from the adhesive layer that contains fentanyl dissolved in an ethanol and water gel. Unlike the fentanyl gel in the Duragesic® reservoir, the fentanyl in the Mylan FTS cannot be physically withdrawn from the patch and cannot be ingested immediately in one dose by cutting or puncturing the patch.[1]

Both the 25 μg/hr Mylan FTS and the 25 μg/hr Duragesic® product contain approximately 2.5 mg of fentanyl. See Declaration of Gordon Flynn, Ph.D ("Flynn Decl.") at ¶ 12. Like Duragesic®, the drug content in the Mylan FTS increases proportionally with increased dosages. Id.

Mylan submitted ANDA 76-258 in December 2001 seeking approval for its generic fentanyl transdermal system. On November 21, 2003, FDA granted final approval of the Mylan FTS as bioequivalent to Janssen's Duragesic® product.[2] Thus, after full agency review, FDA found that the Mylan FTS meets all applicable safety standards and in its June 22, 2004 letter to Mylan, the agency confirmed that "the drug is safe and effective for use as recommended in the submitted labeling." None of the facts that led FDA to reach that conclusion in its November 21, 2003 letter and again in its

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[1] For that reason, the safety concerns relating to puncturing or cutting the patch to release fentanyl gel that are raised in the Comments by the Drug Free America Foundation, Inc. and Drug Free Schools Coalition are inapplicable to the Mylan FTS.

[2] This final approval was rescinded on June 22, 2004 and converted to tentative approval for reasons relating to the patent litigation, none of which involved safety or efficacy issues.

June 22, 2004 letter to Mylan have changed. FDA has never expressed concerns about abuse or diversion of the Mylan FTS relating to, or because of, its design.

As part of the approval process, Mylan submitted, and FDA approved, labeling for the Mylan FTS. Like Duragesic®, the Mylan FTS is a DEA schedule CII product and, therefore, its distribution is strictly controlled to prevent and detect diversion. The approved labeling for the Mylan FTS reflects FDA's consideration of abuse and diversion issues relating to fentanyl transdermal systems by including, inter alia, multiple warnings about the dangers of misuse of fentanyl transdermal systems, warnings about the proper disposal of unused fentanyl transdermal systems, warnings not to cut the patch, and cautions about the illegality of providing fentanyl transdermal systems to anyone other than the patient for whom it was prescribed.

Beginning with the initial quota request in April 1999 and throughout the development and approval of the Mylan FTS, Mylan has also been in close contact with the Drug Enforcement Administration ("DEA") concerning its product. DEA is the agency primarily responsible for assessing the abuse and diversion risks of drug products. See DEA Mission Statement at **www.dea.gov/agency/mission.htm**. As part of that process DEA has been informed of the nature of the Mylan FTS and its drug content. During a meeting with DEA on December 17, 2003, in Washington D.C., representatives of DEA including Ms. Christine A. Sannerud, Ph.D, Deputy Chief, Drug and Chemical Evaluation Section, requested Mylan to address the potential abuse of Mylan FTS. DEA's only expressed concern was whether there was a risk that fentanyl could be physically withdrawn from the patch (as can occur in Duragesic®). Mylan presented DEA with a detailed analysis of the design of Mylan FTS and explained that its product did not contain fentanyl gel, and therefore, would not be subject to that type of leakage or extraction. In fact, Mylan explained to DEA that the Mylan FTS would be subject to less abuse than Duragesic® because of the lack of any

reservoir of fentanyl gel. Since that meeting, DEA has never raised any concerns about the potential abuse or diversion issues arising from the Mylan FTS. Thus, the two agencies charged with addressing the safety and potential abuse and diversion risks have not found any basis to raise concerns about the design of the Mylan FTS.

- **The Mylan Fentanyl Transdermal System is Not An Abuse or Diversion Risk**

As the Petitioners acknowledge, neither the Duragesic® product nor the Mylan FTS when used as directed as sustained release transdermal patches present abuse or diversion risks. FDA and DEA did raise issues about the potential abuse or diversion of fentanyl transdermal systems during the development and approval process for Duragesic®. Those issues were resolved, because FDA concluded that Alza had successfully addressed potential abuse issues by minimizing the amount of drug in the patch. See Petition at 9. Alza shared the view that the abuse and diversion issues presented by fentanyl transdermal systems were addressed by Duragesic®'s minimization of the amount of drug in the patch. See Testimony of Dr. Mary Southam, Alza's Vice President of Technology Assessment (Exhibit 2 to Flynn Declaration). Because the Mylan FTS contains essentially the same amount of fentanyl as the comparable Duragesic® product and delivers a bioequivalent amount of fentanyl, see Flynn Decl. at ¶¶ 11-12, FDA's conclusion that potential abuse issues relating to Duragesic® had been successfully addressed by minimizing the amount of the drug was equally applicable to the Mylan FTS.

- **Mylan's Fentanyl Transdermal System Does Not Become A Rapid Release Product If Placed In the Mouth.**

The essence of the Petition submitted by Drs. Brookoff and Voth is a request that FDA reconsider its determination that the Mylan FTS, like other fentanyl transdermal systems using low drug loading, is safe and effective under its current proposed labeling. The basis for the Petition is the assertion that the sustained release aspect of the Mylan fentanyl transdermal system would be

overcome and it would become a "fast release" system if it were (1) cut into pieces and (2) placed in the mouth rather than on the skin. See Petition at 11. This assertion is based on a fundamental misunderstanding of the science underlying the Mylan fentanyl transdermal system. The Petitioners appear to believe that if cut into pieces and placed in the mouth, the Mylan FTS would deliver fentanyl rapidly into the bloodstream and even contend that the fentanyl in the system would be "immediately" available. That is simply incorrect. The Mylan FTS would be a very inefficient vehicle for delivering fentanyl through the buccal membranes in the mouth. Even if cut into pieces and placed in the mouth, the Mylan FTS matrix remains a slow-release delivery system and the basic mechanism of delivery of fentanyl does not change. See Flynn Decl. at ¶ 15. Fentanyl still has to diffuse to the patch's releasing surface before partitioning into the oral fluids, a slow process controlled by fentanyl's solubility in and diffusion coefficient through the patch's adhesive matrix. Id. In contrast to Duragesic®, which if cut into pieces would leak gel containing dissolved fentanyl, cutting the Mylan FTS into pieces would just result in smaller pieces of drug-containing adhesive.

Cutting a Mylan FTS into smaller pieces does not in any way increase the rate of fentanyl delivery from each square centimeter of the system. Flynn Decl. at ¶ 16. In fact, because dosing from transdermal systems is proportional to the surface area of the system, the effect of cutting the system into smaller pieces would be to reduce the possible fentanyl delivery from that system proportionally. Id. In other words, cutting a Mylan FTS in half would reduce its surface area by half and therefore halve the dose of fentanyl potentially delivered from that system. Placing a Mylan FTS in the mouth rather than on the skin (whether it was cut into pieces or not) would not deliver fentanyl rapidly so as to make it an attractive target for abuse. First, the silicone adhesive in the Mylan FTS would not adhere to the oral mucosa. See Flynn Decl. at ¶ 18. In fact, the extremely hydrophobic nature of that adhesive means that it is particularly ill-suited for maintaining contact between the matrix and the buccal

membrane. Id. at 18-21. This conclusion is supported by the fact that products that are designed to be adhered to oral surfaces use entirely different types of adhesives, ones that are extremely hydrophilic, not hydrophobic. Flynn Decl. at ¶ 21. Intimate contact between a matrix system and the membrane (whether it is skin or a mucosal membrane) is essential to allowing the system to deliver drug rapidly to the bloodstream. Id. at ¶ 18.

Because of the lack of adhesion, rather than moving quickly into the bloodstream, any fentanyl released by the system in the mouth is likely to end up at extremely low concentrations in the saliva. Flynn Decl. at ¶ 22. Fentanyl in the saliva that is swallowed will not have significant systemic effects because of the high first-pass metabolism of fentanyl. Id. at ¶ 23. Therefore, a potential abuser would not be able to place the Mylan FTS against the inside of his cheek and receive rapid delivery of fentanyl.

Second, the fentanyl base contained in the Mylan FTS would not be immediately released from the system if it were placed in the hydrophilic environment of the mouth. Flynn Decl. at ¶ 25. The Mylan FTS contains the base form of fentanyl, a highly water-insoluble component, in a water-insoluble silicone adhesive backed by a water insoluble polymeric film. Id. Most of the fentanyl base contained in the Mylan FTS is undissolved drug. Id. As a result, although some fentanyl would be released from the Mylan FTS into the mouth, that release would be far from an immediate release of the drug load. In fact, drug release would likely be quite slow because of the slow dissolution of fentanyl base in water. Id. at ¶¶ 24-25.

Dissolution data on the Mylan FTS confirms that it would not release fentanyl rapidly in the watery environment of the mouth. In dissolution testing, when placed in water at physiologic pHs, the Mylan FTS released only 15 percent of its drug in 30 minutes. Flynn Decl. at ¶ 24. Based on this data, it is clear that the vast majority of the drug in the Mylan FTS would not be dissolved out of the matrix

after 30 minutes. Therefore, even if the entire Mylan FTS were placed in the mouth, the amount of fentanyl released from the system in a half hour is less than the amount delivered from Actiq®.

Based on these basic facts about the design of the Mylan FTS, the matrix, if placed in the mouth, would provide a slow and steady release of fentanyl with low efficiency in reaching the bloodstream. See Flynn Decl. at ¶ 25. The literature on abuse of prescription drugs makes plain that the abuse and diversion potential of a drug is directly related to its ability to provide users with a rapid increase in the levels of drug inside the brain. See Declaration of H. Brian Goldman, M.D. ("Goldman Decl.") at ¶ 5. A rapid increase in opioid levels in the brain will trigger a rapid increase in dopamine in the brain, producing euphoria or pleasure of rapid onset. Id. Therefore, a system with a slow pattern of delivering opioids would not create a desirable rapid increase in the levels of the drug inside the brain and, therefore, would not be an attractive target for abusers. Id. at ¶ 6.

- **The Mylan Fentanyl Transdermal System Is An Entirely Different Formulation than Actiq®**

The Petition's use of Actiq® as an example of what might occur if the Mylan FTS were available to addicts ignores the fundamental differences between the two products. Actiq® is a fentanyl lozenge designed to be placed against the inside of the cheek for quick relief of severe breakthrough pain experienced by cancer patients. It delivers in just minutes more fentanyl than is delivered over the course of an hour by the largest fentanyl transdermal systems on the market.

Actiq® presents an abuse or diversion issue because when used as designed it provides rapid delivery of high doses of fentanyl within minutes. See Flynn Decl. at ¶ 26. Actiq®'s labeling indicates that it is designed to deliver its entire drug load in less than 15 minutes. See Flynn Decl. at ¶ 28. That sort of rapid release of an opioid like fentanyl is precisely the kind of release pattern that is particularly attractive to abusers. See Goldman Decl. at ¶ 5.

To accomplish its goal of providing rapid relief from breakthrough cancer pain, Actiq® was particularly designed for rapid delivery of fentanyl in the hydrophilic environment of the mouth. Rather than using the insoluble fentanyl base, Actiq® uses soluble fentanyl citrate. That fentanyl citrate is contained not in the insoluble silicone adhesive used in the Mylan FTS but in extremely soluble candy-like form. See Flynn Decl. at ¶¶ 27-28. In short, Actiq®'s design is the polar opposite of the Mylan FTS in terms of its ability to deliver fentanyl through the oral mucosa rapidly. For that reason, the studies cited by Petitioners concerning the effects of the delivery of fentanyl after the rapid delivery obtained from Actiq® do not provide an indication of the effects of the much slower delivery that could possibly be obtained from the Mylan FTS.

- **The Mylan Fentanyl Transdermal System Does Not Present an Abuse Risk Similar to OxyContin®**

Petitioners' reliance on OxyContin® as an example of the type of risk posed by the Mylan FTS is misplaced. OxyContin®, like the Mylan FTS, is designed to be used for controlled-release of an opioid. However, the similarities end there. OxyContin® is designed as a controlled-release oral tablet. The controlled-release properties of OxyContin® are easily circumvented by simply crushing or dissolving that tablet. Goldman Decl. at ¶ 7. When crushed or dissolved, the entire dose of oxycodone is converted to a form that can be absorbed rapidly by the oral, nasal or intravenous routes. Id. Thus, OxyContin® does present the very problem identified by Petitioners: a controlled-release dosage form containing a high drug load that is easily convertible into an immediately available dose of opioids.

As discussed above, the Mylan FTS cannot be converted by abusers into an immediately available dose of opioids. Therefore, it simply does not present the same kind of attractive target for abuse that OxyContin® presents. See Goldman Decl. at ¶ 9.

- **Janssen's Experiences with Solid Matrices Do Not Raise Abuse Concerns**

Mylan is not privy to Janssen's FDA filings concerning its matrix fentanyl transdermal patch and, therefore, is not aware of the specific formulation Janssen proposed to use. However, the suggestion by Petitioners that Janssen withdrew its applications for such a patch out of concern about potential abuse and diversion issues is inconsistent with Janssen's actions in bringing that very type of product to market in Europe, under the product name Durogesic-SMAT®. See Flynn Decl. at ¶ 29. Recognizing the advantages of a matrix patch, including the elimination of the dangers of gel leakage, Janssen is removing the reservoir product from the market as its new matrix product is approved. See Citizens' Petition 2004P-0506 at 3. The experience to date with Janssen's product in Germany does not support the speculation that monolithic fentanyl transdermal systems will be subject to particular abuse. Dr. Goldman's review of the literature did not reveal any published reports of abuse of Janssen's European monolithic fentanyl transdermal systems in any of the ways posited by Petitioners to be a risk. See Goldman Decl. at ¶ 11.

- **Nothing about the Reservoir Design Employed by Duragesic® Makes it Less Abusable than a Solid State Matrix System**

The Petition's assertion that the reservoir design of Duragesic® prevents its abuse is unsupported in the record of FDA and DEA's analysis of the abuse potential associated with Duragesic®. The subject of abuse potential as it relates to the design and development of Duragesic® was a point of significant testimony at the patent trial and nowhere in the extensive record presented at the patent trial, summarized in the Petition at pages 8-9, is there any suggestion that FDA or DEA believed that the reservoir design reduced the likelihood of abuse. To the contrary, FDA asked that Alza demonstrate that the amount of fentanyl that could be physically withdrawn from its used patches be below the euphoric dose. Based on the conclusion that abusers could not physically withdraw

euphoric doses from the reservoir due to the minimization of drug used in the patch, FDA concluded that the abuse issue had been addressed. See Petition at 8-9. The Mylan FTS contains no more fentanyl than that in Duragesic®, irrespective of whether fresh or used patches are compared.

Not only does the Mylan FTS not pose a substantial risk of abuse under the scenarios posited by Drs. Brookoff and Voth, it eliminates some of the very dangerous and potentially deadly routes of abuse they have identified with Duragesic®. See Petition at 7 (collecting literature concerning deaths attributable to abuse of Duragesic®). Because there is no reservoir containing fentanyl-laden gel that can be easily withdrawn from the system, the Mylan FTS presents no risk that addicts will attempt to withdraw that gel and inject it. Because the rate controlling mechanism in the Mylan FTS is not dependent on the integrity of a fragile membrane, there are no dangers from leaking gel or punctured systems that would overcome the controlled release design of the transdermal system. Although abusing Duragesic® through physically withdrawing the fentanyl-containing gel may be fairly rare as Petitioners suggest, elimination of that potentially deadly practice through introduction of the solid state matrix patch would be an additional benefit of the Mylan FTS. See Goldman Decl. at ¶ 12. Because the Mylan FTS eliminates these specific abuse concerns and does not offer an attractive alternative for potential abusers, the abuse potential for the Mylan FTS is lower than that for Duragesic®. Petitioners' own manuscript, which concludes that the abuse potential for Duragesic® is very low, indicates that the Mylan FTS would also have a very low potential for abuse.

## CONCLUSION

For the reasons set forth herein, the Petition should be denied.

Respectfully submitted,

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